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L1	immobil$ same nucleic same biochip$	15	L1
L2	immobiliz$ same nucleic same biochip$	15	L2
L3	immobiliz$ same nucleic same biochip$ same double same strand$	1	L3
L4	immobiliz$ same nucleic same biochip$ same double same strand$ same cryatal	0	L4
L5	immobiliz$ same nucleic same biochip$ same double same strand$ same crystal	0	L5
L6	immobiliz$ same dna same biochip$ same double same strand$ same crystal	0	L6
L7	immobiliz$ same dna same biochip$ same double same strand$	0	L7
L8	immobiliz$ same dna same biochip$ same double same strand$	0	L8
L9	immobiliz$ same dna same biochip$ same double same single$	0	L9

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IMMOBILIZABLE.USPT.	240
IMMOBILIZABLY.USPT.	11
IMMOBILIZABLY-LABELLED.USPT.	1
IMMOBILIZABLY-MODIFIED.USPT.	2
IMMOBILIZAION.USPT.	1
IMMOBILIZAITON.USPT.	2
IMMOBILIZALE.USPT.	1
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IMMOBILIZABLY-LABELLED.USPT.	1
IMMOBILIZABLY-MODIFIED.USPT.	2
IMMOBILIZAION.USPT.	1
IMMOBILIZAITON.USPT.	2
IMMOBILIZALE.USPT.	1
(IMMOBILIZ$ SAME NUCLEIC SAME BIOCHIP$ SAME DOUBLE SAME STRAND$).USPT.	1

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☐ 1. Document ID: US 6365418 B1

L1: Entry 1 of 15 File: USPT Apr 2, 2002

DOCUMENT-IDENTIFIER: US 6365418 B1
TITLE: Arrays of protein-capture agents and methods of use thereof

Brief Summary Paragraph Right (9):
Miniaturized DNA chip technologies have been developed (for example, see U.S. Pat. Nos. 5,412,087, 5,445,934, and 5,744,305) and are currently being exploited for the screening of gene expression at the MRNA level. These chips can be used to determine which genes are expressed by different types of cells and in response to different conditions. However, DNA biochip technology is not transferable to protein-binding assays such as antibody assays because the chemistries and materials used for DNA biochips are not readily transferable to use with proteins. Nucleic acids such as DNA withstand temperatures up to 100.degree. C., can be dried and re-hydrated without loss of activity, and can be bound physically or chemically directly to organic adhesion layers supported by materials such as glass while maintaining their activity. In contrast, proteins such as antibodies are preferably kept hydrated and at ambient temperatures are sensitive to the physical and chemical properties of the support materials. Therefore, maintaining protein activity at the liquid-solid interface requires entirely different immobilization strategies-than those used for nucleic acids. The proper orientation of the antibody or other protein at the interface is desirable to ensure accessibility of their active sites with interacting molecules. With miniaturization of the chip and decreased feature sizes, the ratio of accessible to non-accessible and the ratio of active to inactive antibodies or proteins become increasingly relevant and important.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

☐ 2. Document ID: US 6365415 B1

L1: Entry 2 of 15 File: USPT Apr 2, 2002

DOCUMENT-IDENTIFIER: US 6365415 B1
TITLE: Method for characterization and quality control of porous media

Brief Summary Paragraph Right (4):
Microfabricated arrays (biochips) of oligonucleotides, nucleic acids, or peptides have utility in a wide variety of applications, including DNA and RNA sequence analysis, diagnostics of genetic diseases, gene polymorphism studies, analysis of gene expression, and studies of receptor-ligand interactions. In the process of biochip fabrication, large numbers of probe molecules are bound to small, defined regions of a substrate. Glass slides, silicon wafers, or polymeric hydrogels may be used as a biochip substrate, with a two-dimensional or three-dimensional substrate surface utilized for probe attachment. As compared to two-dimensional biochip substrates, three-dimensional substrates offer an advantage of increased

sensitivity. This increased sensitivity results from the larger surface area of three-dimensional substrates, allowing for the immobilization of a greater number of probe molecules in a fixed two-dimensional area, and in turn permitting the interaction of a greater number of bound probe molecules with target molecules (biomolecules) in a given sample.

Detailed Description Paragraph Right (4):
It will be understood by those with skill in the art that the method of the present invention is advantageously practiced on porous hydrogel substrates being used in the commercial production of bioarrays fabricated from porous hydrogel substrates. As used herein, the terms "bioarray," "biochip" and "biochip array" refer to an ordered spatial arrangement of immobilized biomolecules or polymeric anchoring structures on a solid supporting substrate. Preferred probe molecules include nucleic acids, oligonucleotides, peptides, ligands, antibodies and antigens; oligonucleotides are the most preferred probe species.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 3. Document ID: US 6361942 B1

L1: Entry 3 of 15 File: USPT Mar 26, 2002

DOCUMENT-IDENTIFIER: US 6361942 B1
TITLE: Method, kits and compositions pertaining to detection complexes

Detailed Description Paragraph Right (72):
One or more of the component polymers which comprise a Detection Complex, Substrate Detection Complex or PCR Detection Complex of this invention may optionally be immobilized to a surface for the purpose of formiing a support bound Detection Complex. The component polymer can be immobilized to the surface using the well known process of UV-crosslinking. Alternatively, the component polymer is synthesized on the surface in a manner suitable for deprotection but not cleavage from the synthesis support (See: Weiler, J. et al., "Hybridization based DNA screening on peptide nucleic acid (PNA) oligomer arrays", Nucl. Acids Res., 25:, 2792-2799 (1997)). In still another embodiment, one or more component polymer is covalently linked to a surface by the reaction of a suitable functional group on the probe with a functional group of the surface (See: Lester, A. et al, PNA array technology. Presented at Biochip Technologies Conference in Annapolis (October, 1997)).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

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☐ 4. Document ID: US 6359125 B1

L1: Entry 4 of 15 File: USPT Mar 19, 2002

DOCUMENT-IDENTIFIER: US 6359125 B1
TITLE: Process for preparing peptide nucleic acid probe using polymeric photoacid generator

Brief Summary Paragraph Right (24):
The peptide nucleic acid synthesis method is generally carried out in a similar manner as the oligonucleotide synthesis method conventionally known in the art(see: Acc. Chem. Res., 24:278, 1991). Nielson et al synthesized oligopeptide nucleic acid

by using solid-phase phase as follows: First, the amino group of solid support is reacted with the carboxyl group of peptide nucleic acid of specified base(A, C, G or T) whose amino group in backbone is protected by acid- or base-labile functional group to link each other in a form of amide bond. Next, the resultant is treated with acid or base to eliminate amino protecting group to reveal amino group, which is subsequently reacted with the carboxyl group of peptide nucleic acid of specified base whose amino group in backbone is protected by acid- or base labile functional group to link each other in a form of amide bond, and, the said steps are repeated to obtain an oligonucleotide of desired base sequence and number, and finally treated with strong acid to separate the exocyclic amino protecting group from solid support by chemical reaction. This method is desirable in a sense that it assures complete reaction of excessive peptide nucleic acids(5 equivalents) as much as possible and easy purification of peptide nucleic acid on an organic solvent-resistant solid support by filtering the residual monomers and reactants and washing with organic solvent. Based on the solid-phase synthesis, the present inventors prepared biochip with various nucleotide sequences to finally prepare arrays of peptide nucleic acid probes immobilized on a solid matrix by employing polymeric PAG process illustrated above.

☐ 5. Document ID: US 6355491 B1

L1: Entry 5 of 15 File: USPT Mar 12, 2002

DOCUMENT-IDENTIFIER: US 6355491 B1
TITLE: Individually addressable micro-electromagnetic unit array chips

Brief Summary Paragraph Right (8):
There are two basic types of biochips, i.e., passive and active. Passive biochips refer to those on which chemical or biochemical reactions are dependent on passive diffusion of sample molecules. In active biochips reactants are actively moved or concentrated by externally applied forces so that reactions are dependant not only on simple diffusion but also on the applied forces. The majority of the available biochips, e.g., oligonucleotide-based DNA chips from Affymterix and cDNA-based biochips from Incyte Pharmaceuticals, belongs to the passive type. There are structural similarities between active and passive biochips. Both types of biochips employ of arrays of different immobilized ligands or ligand molecules. Herein, "ligands or ligand molecules" refers to bio/chemical molecules with which other molecules can react. For instance, a ligand may be a single strand of DNA to which a complementary nucleic acid strand can hybridize. A ligand may be an antibody molecule to which the corresponding antigen (epitope) can bind. A ligand may also include a particle on whose surface are a plurality of molecules to which other molecules may react. By using various markers and indicator molecules (e.g.: fluorescent dye molecules), the reaction between ligands and other molecules can be monitored and quantified. Thus, an array of different ligands immobilized on a biochip enables the reaction and monitoring of multiple analyte molecules.

Brief Summary Paragraph Right (19):
The present invention further discloses methods for manipulating biomolecules/bioparticles, chemical-reagent molecules, drug molecules or any other molecules or particles with an electromagnetic biochip. These biochips can generally be used to manipulate any kind of magnetic particle. For controlling and handling non-magnetic particles and/or biomolecules, these materials are first magnetically modified. For example, the molecules may be covalently attached or physically absorbed to the surface of magnetic particles. The biomolecules may be proteins (e.g., antibodies, antigens and receptors), nucleic acids (e.g., single stranded DNA or RNA) or other molecules such as lipids or carbohydrates. The electromagnetic biochip surface may be modified for immobilizing ligand molecules that are capable

of interacting with molecules on the surface of the manipulated magnetic particles. Such interactions are facilitated because the magnetic particles are concentrated at specific locations on which the appropriate ligand molecules are already immobilized.

Detailed Description Paragraph Right (7):
The functional layer 42 shown on the chip surface of FIG. 1 is used for immobilizing ligand molecules. It may be a hydrophilic or hydrophobic molecular monolayer, a hydrophilic or hydrophobic membrane, a hydrophilic or hydrophobic gel, a polymer layer, porous or non-porous materials and/or the composite of these materials. Molecular monolayer refers to single molecular layer (for example, Langmuir-Blodgett film as can be formed in a Langmuir trough). For immobilizing nucleic acid ligands, binding materials such as nitrocellulose or nylon may be used as in Southern or northern blots. Proteins and peptides can be bound by various physical (e.g., hydrophobic) or chemical approaches. For example, specific receptors such as antibodies or lectins can be incorporated into the functional layer 42 for binding ligand molecules of protein or peptide-types. Depending on the intended ligand and the assays or reactions to be carried out by the biochip, different molecules can be incorporated into the functional layer 42 for binding ligand molecules. These molecules incorporated in the functional layer 42 for binding ligand molecules are referred to as the functional groups. Examples of the functional groups include, but not limited to aldehydes, carbodiimides, succinimydyl esters, antibodies, receptors, and lectins. The functional groups also include chemical groups or molecular sites that are formed through chemical modification on the chip surface molecules. The methods of using the electromagnetic biochips 10 will be described in later sections of this description.

Detailed Description Paragraph Right (20):
After the micro-electromagnetic array chips are fabricated, the surface of top insulation layer 32 may be chemically modified or may be coated with a thin film layer. This layer is called functional layer 42, which is used for immobilizing ligand molecules. Illustrated in FIG. 13, the functional layer 42 may be hydrophilic or hydrophobic molecular monolayer, a hydrophilic or hydrophobic membrane, a hydrophilic or hydrophobic gel, a polymer layer, or the composite of these materials, as described in the section related to FIG. 3. The functional layer may be made of porous or non-porous materials. The functional layer 42 may incorporate specific molecules such as antibodies for binding ligand molecules, depending on the intended ligand and the assays or reactions to be carried out on the biochip. These molecules incorporated in the functional layer for attaching or binding ligand molecules are referred to as functional groups. For immobilizing nucleic acid ligands binding materials such as nitrocellulose or nylon, polylysine, agarose gel, hydrogel, acrylamide gel as used in Southern or northern blots may be used as functional layers. For immobilizing proteins and peptides, antibodies or other protein molecules may be incorporated into the functional layer 42 and used as the functional groups.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments

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☐ 6. Document ID: US 6329209 B1

L1: Entry 6 of 15 File: USPT Dec 11, 2001

DOCUMENT-IDENTIFIER: US 6329209 B1
TITLE: Arrays of protein-capture agents and methods of use thereof

Brief Summary Paragraph Right (9):
Miniaturized DNA chip technologies have been developed (for example, see U.S. Pat. Nos. 5,412,087, 5,445,934, and 5,744,305) and are currently being exploited for the screening of gene expression at the mRNA level. These chips can be used to determine

which genes are expressed by different types of cells and in response to different conditions. However, DNA biochip technology is not transferable to protein-binding assays such as antibody assays because the chemistries and materials used for DNA biochips are not readily transferable to use with proteins. Nucleic acids such as DNA withstand temperatures up to 100.degree. C., can be dried and re-hydrated without loss of activity, and can be bound physically or chemically directly to organic adhesion layers supported by materials such as glass while maintaining their activity. In contrast, proteins such as antibodies are preferably kept hydrated and at ambient temperatures are sensitive to the physical and chemical properties of the support materials. Therefore, maintaining protein activity at the liquid-solid interface requires entirely different immobilization strategies than those used for nucleic acids. The proper orientation of the antibody or other protein at the interface is desirable to ensure accessibility of their active sites with interacting molecules. With miniaturization of the chip and decreased feature sizes, the ratio of accessible to non-accessible and the ratio of active to inactive antibodies or proteins become increasingly relevant and important.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 7. Document ID: US 6310687 B1

L1: Entry 7 of 15 File: USPT Oct 30, 2001

DOCUMENT-IDENTIFIER: US 6310687 B1
TITLE: Light detection device with means for tracking sample sites

Detailed Description Paragraph Right (39):
Representative sample holders include microplates, PCR plates, biochips, and chromatography plates, among others. A microplate is a multi-well sample holder, typically but not exclusively used for luminescence applications. A PCR plate is a multi-well sample holder used for performing PCR. Preferred PCR plates would include a footprint, well spacing, and well shape similar to those of the preferred microplates, while possessing a stiffness adequate for automated handling and a thermal stability adequate for PCR. A biochip is a small, flat surface (such as a glass or silicon wafer, a semiconductor chip, or a multiple-well CCD) onto which biomolecules (such as nucleic acids and proteins) are immobilized in distinct spots or arrays. Biochips include DNA chips, DNA microarrays, gene arrays, and gene chips, among others. Preferred biochips are described in Bob Sinclair, Everything's Great When It Sits on a Chip: A Bright Future for DNA Arrays, 13 The Scientist, May 24, 1999, at 18. As defined here, a chromatography plate is a flat surface used for performing chromatography, electrophoresis, or other separations.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 8. Document ID: US 6280946 B1

L1: Entry 8 of 15 File: USPT Aug 28, 2001

DOCUMENT-IDENTIFIER: US 6280946 B1
TITLE: PNA probes, probe sets, methods and kits pertaining to the universal detection of bacteria and eucarya

Detailed Description Paragraph Right (26):
One or more of the PNA probes of this invention may optionally be immobilized to a

surface for the detection of the target sequence of bacteria and/or eucarya. Generally, surface immobilized PNA probes can be used in a capture assay. PNA probes can be immobilized to the surface using the well known process of UV-crosslinking. More preferably, the PNA probe is synthesized on the surface in a manner suitable for deprotection but not cleavage from the synthesis support (See: Weiler, J. et al, Hybridization based DNA screening on peptide nucleic acid (PNA) oligomer arrays., Nucl. Acids Res., 25:2792-2799 (July, 1997)). In still another embodiment, one or more PNA probes are covalently linked to a surface by the reaction of a suitable functional group on the probe with a functional group of the surface (See: Lester, A. et al, "PNA Array Technology": Presented at Biochip Technologies Conference in Annapolis (October, 1997)). This method is most preferred since the PNA probes on the surface will typically be highly purified and attached using a defined chemistry, thereby minimizing or eliminating non-specific interactions.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 9. Document ID: US 6261783 B1

L1: Entry 9 of 15 File: USPT Jul 17, 2001

DOCUMENT-IDENTIFIER: US 6261783 B1
TITLE: Homogeneous detection of a target through nucleic acid ligand-ligand beacon interaction

Detailed Description Paragraph Right (73):
In another embodiment, the target-binding nucleic acid, containing the binding site for the target molecule, is immobilized on the surface of a solid support, such as a biochip. The nucleic acid is attached at either the 3' or the 5' end to functional groups displayed on the surface of the biochip. Methods for attaching nucleic acids to biochips are well known in the art, and include methods for attaching different nucleic acids to discrete locations on the same biochip. The biochip is then contacted with a test mixture suspected of containing target molecules to which the first nucleic acid can bind. Following removal of unbound material from the biochip by washing, the biochip will be contacted with a solution containing the three sets of nucleic acids labeled as described above with an energy transfer pair. If the biochip-bound nucleic acid binds to target molecule, then a multimolecular complex will form on the biochip. The presence of this complex can be detected by measuring fluorescence on the biochip. Such a biochip can be used to detect exceedingly rare molecules in test mixtures, and will have utility in diagnostic and prognostic medical screening, and in environmental testing.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

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☐ 10. Document ID: US 6242246 B1

L1: Entry 10 of 15 File: USPT Jun 5, 2001

DOCUMENT-IDENTIFIER: US 6242246 B1
TITLE: Nucleic acid ligand diagnostic Biochip

Drawing Description Paragraph Right (5):
FIG. 5 depicts a mechanism for detection of target molecule binding in which a Nucleic acid ligand containing an additional binding site for a small molecule is immobilized on a Biochip.

Detailed Description Paragraph Right (16):
As described in the SELEX patent applications, it is possible to create Nucleic acid ligands with constant and random sequence regions. In a particularly preferred embodiment, Nucleic acid ligands will be synthesized that have a common short sequence (seq. A) located at a predetermined position. The initial candidate mixture of Nucleic acids will then be contacted with a solid support, preferably a column, containing an immobilized Nucleic acid (seq. A') complementary in sequence to the common short sequence on each ligand. The pool of ligands will then bind to the column through complementary base pairing between A and A'. A mixture containing the Target molecule(s) will then be passed over the column, and ligands that are displaced from the column will be collected. The displacement of these ligands indicates that the binding of the Target molecule alters the conformation of the ligand in such a manner that the common short sequence is no longer able to bind to its complementary sequence. In a related embodiment, the initial candidate mixture of Nucleic acid ligands will be contacted with Target molecule, and binding will be allowed to occur in solution phase. The Nucleic acid ligands will then be contacted with the column described above. Nucleic acid ligands that have bound Target in such a way that sequence A is not able to hybridize to column-bound sequence A' will pass through the column, and can be collected. The Nucleic acid ligands obtained in these two embodiments will be used in the Biochip as described in detail below in the section entitled "Detection of Target Molecule Binding to Nucleic Acid Ligand Using Fluorescence Techniques".

Detailed Description Paragraph Right (19):
The production of Biochips on which Nucleic acids are immobilized is well known in the art. The Biochip may be a Langmuir-Bodgett film, functionalized glass, germanium, silicon, PITE, polystyrene, gallium arsenide, gold, silver, or any other material known in the art that is capable of having functional groups such as amino, carboxyl, thiol or hydroxyl incorporated on its surface. Preferably, these groups are then covalently attached to crosslinking agents, so that the subsequent attachment of the Nucleic acid ligands and their interaction with Target molecules will occur in solution without hindrance from the Biochip. Typical crosslinking groups include ethylene glycol oligomer, diamines, and amino acids. Any suitable technique useful for immobilizing a Nucleic acid ligand to a Biochip is contemplated by this invention.

Detailed Description Paragraph Right (28):
In another embodiment, Target molecule binding will be detected using a competition assay, well known to those skilled in the art. Following contacting of the Biochip-bound Nucleic acid ligands with the Test mixture, a solution containing a predetermined amount of each Target for which binding data is sought is added. These Target molecules are fluorescently labeled by any of the ways known in the art in order to permit their detection. The labeled Target molecules compete for binding to the immobilized Nucleic acid ligand. An equilibrium will be established, and the amount of labeled molecule bound at each site will be used to calculate the amount of each Target molecule contained within the original Test mixture.

Detailed Description Paragraph Right (29):
In certain preferred embodiments (FIG. 2), Nucleic acid ligands (21) containing a constant sequence associated with the binding site for the Target molecule will be localized to specific regions of a Biochip (22). The synthesis of such Nucleic acid ligands is described above in the section entitled "Obtaining Nucleic Acid Ligands For Use on a Biochip". The Biochip-bound Nucleic acid ligands will then be hybridized with an oligonucleotide (23) complementary in sequence to the constant region. Contacting this Biochip with a Test mixture will lead to displacement (24) of oligonucleotide from Nucleic acid ligands that bind to their Target molecule (25). In a further embodiment (FIG. 3), a Biochip (31) will be synthesized upon which the complementary oligonucleotide (32) is immobilized by any of the methods known in the art. The Nucleic acid ligands (33) will then be deposited at specific locations on the Biochip, whereupon they will become associated with the oligonucleotide by base pairing. The Biochip will then be contacted with the Test mixture. Target molecule binding (34) will lead to the disruption of base paring between the Nucleic acid ligand and the support bound oligonucleotide (35), and hence displacement of the Nucleic acid ligand from the Biochip will occur.

Detailed Description Paragraph Right (34):
In another embodiment, SELEX will be performed using a pool of Nucleic acids containing a binding site for a particular small molecule. An example of such a small molecule is the caffeine analogue theophylline. Single stranded Nucleic acid ligands against this molecule form a double-stranded stem with a hairpin loop in which the 5' and 3' ends of the molecule are close to one another. This structure only forms in the presence of theophylline. In this embodiment, a candidate mixture of theophylline ligands will be synthesized with random sequence in the hairpin loop. region, and the candidates will then be passed over a solid support, preferably a column, to which theophylline has been attached. The candidate ligands will bind tightly to theophylline, and will become immobilized on the column. The mixture containing Target molecules will be added to the column, and ligands that are eluted will be collected. This will select for ligands that bind their Target molecules in such a way that the ligand will no longer bind to theophylline. Such ligands will be displaced because the adoption of the structure that binds the Target molecule will disrupt the structure that binds the theophylline. The ligands will be refined in the standard ways described in the SELEX patent applications. A Biochip (FIG. 4) will then be fabricated (41) on which theophylline (42) is attached by any of the methods known in the art One or more individual species of the Nucleic acid ligands (43) will then be attached at defined locations on the Biochip, where they bind tightly to the theophylline. Contacting of the Test mixture with the Biochip leads to the displacement (44) from the Biochip of Nucleic acid ligands that bind to their cognate Target molecule (45). The displacement will be detected by any of the means detailed above (46). This technique will be used with any Nucleic acid ligand that forms a hairpin-type structure similar to theophylline, or any other Nucleic acid ligand that can be synthesized with additional random sequence, and will then bind to two different compounds in a mutually exclusive manner, such that the binding of one compound will displace the other.

Detailed Description Paragraph Right (37):
McGall et al., supra, suggest a technique for simultaneously identifying multiple Target Nucleic acid sequences using multiple probes. In the method contemplated, a first set of labeled probes against specific Targets is synthesized, with each probe containing an additional sequence that is unique for that particular probe. These unique sequences are complementary to a second set of oligonucleotides immobilized on a Biochip. The authors envision contacting the Target and the first set of probes in solution, then adding the complexes formed to the Biochip. The additional unique sequence region of each probe will localize that complex to a specific address on the Biochip via its interaction with the second probe bound at that site. Because there are methods known in the art that can be used to partition bound Nucleic acid ligand from unbound, this technique can be applied to the instant invention. Specifically, Nucleic acid ligands will be synthesized with an additional sequence that will be different for each species of Nucleic acid ligand and will preferably be distant from the residues important for the specific binding interaction. The Biochip will contain oligonucleotides with sequence complementary to the unique region of each Nucleic acid ligand species. Each Nucleic acid ligand will also have a detectable group, such as a fluorophore and/or a means for linking the Nucleic acid ligand to another detectable molecule as described above. Alternatively, the second set of Biochip-localized Nucleic acids and the Nucleic acid ligands themselves can be labeled in such a way that they form an energy transfer pair, as described above.

Detailed Description Paragraph Right (40):
In a preferred embodiment, a set of mutually-complementary stem-loop Nucleic acids will be synthesized. A Nucleic acid ligand will be designed with a stem-loop structure, in which the Target molecule binding site is located in the loop region. Each said species of Nucleic acid ligand will be immobilized at discrete locations on the Biochip. The stem region will comprise two partially complementary "arms" of sequence A and B (FIG. 6) that can undergo limited pairing to form an imperfect intramolecular double helix (61). This Nucleic acid ligand will undergo a structural change upon Target molecule binding such that the stem region is completely disrupted (62). Three or more further sets of imperfect stem-loop Nucleic acids will also be synthesized. The first further set will be identical to the Biochip-bound Nucleic acid ligand, but will not contain the Target molecule binding site in the

loop region (63). The sequences of the stem regions of the latter two sets are represented as C'/A' (64) and B'/C (65), and are chosen so that they can bind perfectly to (i) one of the arms of the Nucleic acid ligand stem (A' pairs perfectly with A, and B' pairs perfectly with B), and (ii) the arms of the second set can bind perfectly to the arms of the third set (C' pairs perfectly with C). The three sets will further comprise a fluorescent group (66) and a quenching group (67) located at positions that are spatially adjacent only when the imperfect stem structure is formed. A Biochip with the stem-loop Nucleic acid ligands will be contacted with a Test mixture, and Target molecule binding will lead to the disruption of the stem region of said Nucleic acid ligands. Both sequences A and B will be available for base-pairing. The Biochip will then be contacted with a solution of all three sets of Nucleic acids. The arms of the stems of these latter Nucleic acids will then hybridize to any Nucleic acid ligand that has undergone a Target-binding reaction (68). Upon binding to the Nucleic acid ligand arms, the stem regions of the second and third set of Nucleic acids will be similarly disrupted, and the unhybridized arms can then hybridize to their complementary sequences. This process is driven by the favorable free energy difference between imperfect and the perfect double helices, and will continue until one of the Nucleic acids is depleted from the solution phase. At each hybridization step, another arm sequence becomes available for complementary base pairing, leading to the ultimate formation of a multimolecular complex of intermolecular double helices. Each hybridization step is accompanied by the spatial separation of the quenching group from the fluorescent group, resulting in a highly fluorescent signal (69) being generated at the site on the Biochip where a single Target molecule originally bound to a single Nucleic acid ligand. In this embodiment, the original fluorescent signal is highly amplified by the cascade of hybridization.

Detailed Description Paragraph Right (41):
In another embodiment, one or more spectroscopically detectable labeled Nucleic acid ligands will be immobilized on Biochips. The synthesis of such ligands is disclosed in Pittner et al U.S. Pat. No. 5,641,629 and U.S. Pat. No. 5,650,275, both of which are specifically incorporated herein by reference. The labels on such ligands undergo a detectable change in fluorescence intensity, fluorescence polarization or fluorescence lifetime upon binding of the Nucleic acid ligand to its Target molecule. Suitable labels include fluorescent labels (e.g. fluorescein, Texas Red), luminescent labels (e.g. luciferin, acridinium esters), energy transfer labels (e.g. fluorescein and tetramethylrhodamine), and near IR labels (e.g. dicyanines, La Jolla Blue dye). Binding of the Target molecule to the labeled ligand will be detected by measuring any change in fluorescence. These include, but are not limited to, changes in fluorescence polarization, fluorescence anisotropy, fluorescence intensity, and fluorescence lifetime. These measurements will be made continuously, or in a dynamic manner. Locations on the Biochip where a difference is detectable will then be known to have bound Target molecules, allowing the quantification of each Target molecule in the Test mixture.

Detailed Description Paragraph Right (55):
Nucleic acid ligand GB41 was isolated from a SELEX experiment against the U251 glioma cell line, as described in U.S. patent application No. 08/434,425, filed May 3, 1995, entitled "Tissue SELEX". Here, the Nucleic acid ligand bears a 5' biotin and is immobilized to a streptavidin coated carboxylmethyl dextran Biochip surface (BIACORE 2000). The proteins are injected across flowcells containing GB41 or a version of GB41 in which the nucleotide sequence is scrambled. The scrambled sequence provides a test of binding specificity for the Nucleic acid ligand. Specific binding was detected to full-length tenascin and to a bacterially expressed protein representing fibronectin type m repeats 3-5, which comprises 12% of the mass of full-length tenascin. These proteins did not bind to the scrambled sequence oligonucleotide. The slow dissociation of full-length tenascin, a hexamer, may result form multivalent interactions on the surface. Experiments established the association and dissociation rate constants for this protein-Nucleic acid ligand interaction The association phase (0-125 sec) was linear due to the large size (1.2 million dalton) of tenascin, which causes slow diffusion into the dextran matrix (mass transport-limited binding). The slow dissociation (125-300 sec) was perhaps due to multivalent interactions that could form between the hexameric protein and the dextran-bound Nucleic acid ligand.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 11. Document ID: US 6218116 B1

L1: Entry 11 of 15 File: USPT Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6218116 B1
TITLE: Method and device for treatment by complexing of a liquid medium

Brief Summary Paragraph Type 1 (3):
a) a support for plural complexing, of the biochip type, is provided on which there are distributed a plurality of discrete coupling sites or zones, separated from each other, in which there are immobilized a plurality of oligonucleotides (anti-ligands) which are respectively different and capable of being complexed with the nucleotide sequences complementary to the nucleic fragment(s), respectively;

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 12. Document ID: US 6197503 B1

L1: Entry 12 of 15 File: USPT Mar 6, 2001

DOCUMENT-IDENTIFIER: US 6197503 B1
TITLE: Integrated circuit biochip microsystem containing lens

Brief Summary Paragraph Right (19):
A target nucleic acid sequence is preferably hybridized with a nucleic acid sequence that is selected for that purpose (bioprobe). As stated earlier, the selected bioprobe is immobilized on a suitable substrate, either on the biochip itself or on a membrane type material that is then contacted or attached to the chip surface. The bioprobe may be labeled with a tag that is capable of emitting light or other non-radioactive energy. Upon hybridization with a target nucleic acid sequence, the hybrid product can be irradiated with light of suitable wavelength and will emit a signal in proportion to the amount of target nucleic acid hybridized, see FIG. 20. The labeled bioprobe may comprise a labeled molecular bioreceptor. Known receptors are advantageous to use because of their known ability to selectively bind with the target nucleic acid sequence. In certain particular examples, the bioreceptor itself may exhibit changes in light emission when its cognate is bound.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments KWIC | Draw Desc | Image

☐ 13. Document ID: US 6174683 B1

L1: Entry 13 of 15 File: USPT Jan 16, 2001

DOCUMENT-IDENTIFIER: US 6174683 B1
TITLE: Method of making biochips and the biochips resulting therefrom

Brief Summary Paragraph Right (1):
The present invention relates to new methods of making biochips and the biochips resulting therefrom. In particular, the new method described herein provides for rapid, simple and cost effective construction of biochips by employing polyurethane-based hydrogels to immobilize biomolecular probes on the substrate. In particular, both organic solvent soluble biomolecules, like peptide nucleic acids (PNAs), and water soluble biomolecules, like DNA, RNA and other oligonucleotides, are easily and efficiently bound to the hydrophilic polymer either before or during polymerization thereof. In addition to the improved method of making the biochips described herein, the biochips themselves have improved characteristics including superior stability providing a much improved shelf-life and greater flexibility in use. For example, the biochips of the present invention are useful for gene discovery, gene characterization, functional gene studies, screening for biological activity and related studies.

☐ 14. Document ID: US 5847019 A

L1: Entry 14 of 15 File: USPT Dec 8, 1998

DOCUMENT-IDENTIFIER: US 5847019 A
TITLE: Photoactivatable polymers for producing patterned biomolecular assemblies

Brief Summary Paragraph Right (6):
However, currently several broad strategies are being applied to the development of patterned surfaces on which multiple antibodies are immobilized. The first involves keeping the different antibodies physically separate throughout the immobilization procedure. The techniques employed range from simply applying the antibodies in individual stripes using a paintbrush, to microwriting, microstamping or microspotting. These methods are simple and flexible, but do not allow for the production of high resolution (submicron) protein patterns. The second strategy uses microlithography to produce active substrate regions formed by selective removal or photochemical conversion of reactive monolayers to produce discrete regions for antibody immobilization. See Amos, R. A. et al. Surface Modification of Polymers by Photochemical Immobilization-A General Method, The 17th Annual Meeting of the Society for Biomaterials, 1-5 May 1991, Scottsdale, Ariz., incorporated herein by reference in its entirety and for all purposes. See Clapper, D. L. et al., Covalent Immobilization of Cell Adhesion Proteins and Peptides to Promote Cell Attachment and Growth of Biomaterials, The 16th Annual Meeting of the Society for Biomaterials, 20-23 May, 1990, Charleston, S.C., incorporated herein by reference in its entirety and for all purposes. See Colby, L. E. et al., Light Activated Polymersfor Flexible Surface Modification, Proceedings of the Medical Design & Manufacturing Conference, Jun. 3, 1992, N.Y., N.Y., incorporated herein by reference in its entirety and for all purposes. See Smithson, R. L. W., et al., Ultrathin Film Characterization: Photoreactive Polyacrylamide, 1 Colloids and Surfaces B: Biointerfaces, pp. 349-355 (1993), incorporated herein by reference in its entirety and for all purposes. See Yan, M.; Cai, S. X.; Wybourne, M. N.; Keana, J. F. W. J. Am. Chem. Soc. 115, 814-816, 1993, incorporated herein by reference in its entirety and for all purposes. See also U.S. Pat. Nos. 4,722,906 (Guire); 5,258,041 (Guire); 5,217,492 (Guire); 4,979,959 (Guire), each patent incorporated herein by reference in its entirety and for all purposes. Modification of surfaces for increased biocompatability as discussed by Amos, Clapper, Guire, Yan, Colby and Smithson, supra, differ from the present invention in that (a) they do not teach photoactivation prior to fabrication of arrays of biomolecules and (b) they do not teach that photoactivatable groups are a part of the structure of the formed photoactivatable polymers. See Bhatia, S. K.; Teixeira, J. L.; Anderson, M.; Shriver-Lake, L. C.; Calvert, J. M.; Georger, J. H.; Hickman, J. J.; Dulcey, C. S.; Schoen, P. E.; Ligler, F. S. Anal. Biochem. 208, 197-205, 1993, incorporated herein

by reference in its entirety and for all purposes. See Eggers, M.; Hogan, M.; Reich, R. K; Lamture, J.; Ehrlich, D.; Hollis, M.; Kosicki, B.; Powdrill, T.; Beattie, K.; Smith, S.; Varma, R.; Gangadharan, R.; Mallik, A.; Burke, B.; Wallace, D. BioTechniques, 17, 516-524, 1994, incorporated herein by reference in its entirety and for all purposes. See also U.S. Pat. Nos. 4,103,073 (McAlear et al.); 4,103,064 (McAlear et al.); 4,562,157 (Lowe et al.), each patent incorporated herein by reference in its entirety and for all purposes. See Ekins, R.; Chu, F.; Biggart, E. Analytica Chemica Acta., 227, 73-96, 1989, incorporated herein by reference in its entirety and for all purposes. Bhatia, Eggers, Lowe, McAlear and Ekins, supra, do not teach deposition and/or patterning of multiple (i.e. different) biomolecules. See also U.S. Pat. Nos. 4,591,570 (Chang), incorporated herein by reference in its entirety and for all purposes. See Kakabakos, S. E.; Christopoulos, T. K.; Diamandis, E. P. Clin. Chem., 38, 338-342, 1992, incorporated herein by reference in its entirety and for all purposes. See Parsons, R. G.; Kowal, R. LeBlond, D.; Yue, V. T.; Neargarder, L.; Bond, L.; Garcia, D.; Slater, D.; Rogers, P. Clin. Chem. 1993, 39, 1899-1903, incorporated herein by reference in its entirety and for all purposes. Chang, Kakabakos, and Parsons, supra, do not use photoactivation to determine the geometry of biomolecular arrays and do not describe a technique for the fabrication of micron scale biomolecular arrays. See Lopez, G. P.; Biebuyck, H. A.; Whitesides, G. M. Langmuir, 9, 1513-1516, 1993, incorporated herein by reference in its entirety and for all purposes. See Pale-Grosdemange, C.; Simon, E. S.; Prime, K. L.; Whitesides, G. J. Am. Chem. Soc., 113, 12-20, 1991, incorporated herein by reference in its entirety and for all purposes. See Prime, K. L.; Whitesides, G. M. J. Am. Chem. Soc. 115, 10714-10721, 1993, incorporated herein by reference in its entirety and for all purposes. Lopez, Pale-Grosdemange, and Prime, supra, only describe production of biomolecular arrays on gold surfaces via chemisorbed thiols. See Pritchard, D. J. et al., Micron-Scale Patterning of Biological Molecules, 34, No. 1, Angew. Chem. Int. Ed. Engl., pp. 91-93, 1995, incorporated herein by reference in its entirety and for all purposes. Pritchard, supra, describes deposition of two antibodies in distinct locations based on photoactivation of an aryl nitrene linked to biotin wherein the biotin moiety is bound to surface bound avidin. Pritchard has to add the aryl nitrene linked biotin (i.e. photoactivatable cross-linker) after deposition of the avidin on the surface of the substrate. In contrast, according to the presently claimed invention, the photoactivatable compound (e.g. 2,6-DOCA-which can be incorporated in any density or concentration desired) is an integral part of the polymer layer. Furthermore, according to the Pritchard technique, supra, the large size (360 Kd molecular weight) of the avidin limits the density of the aryl nitrene biotin bound to the substrate surface. See Fodor, S. P. A. et al., Light-Directed, Spatially Addressable Parallel Chemical Synthesis, Research Article, pp. 767-773, 15 Feb., 1991, incorporated herein by reference in its entirety and for all purposes. Fodor, supra, describes a method for the deposition of nucleic acid polymers or peptides upon a substrate, respectively. However, the deposition technique of Fodor, supra, requires that the deposition of the nucleic acid polymer or peptide be done one base pair or one amino acid at a time, respectively. See Smithson, R. L. W., et al., Ultrathin Film Characterization: Photoreactive Polyacrylamide, 1 Colloids and Surfaces B: Biointerfaces, pp. 349-355 (1993), incorporated herein by reference in its entirety and for all purposes. See also Wrotnowski, C., Biochip Technology Offers Powerful Tools for Reasearch and Diagnostics, Genetics and Engineering News, 15 Nov., 1994 at page 8, incorporated herein by reference in its entirety and for all purposes. See also U.S. Pat. Nos. 4,591,570 (Chang); 4,751,171 (Ogawa); 4,103,073 (McAlear et al.); 4,103,064 (McAlear et al.); 4,562,157 (Lowe et al.); 4,722,906 (Guire); 5,258,041 (Guire); 5,217,492 (Guire); 4,979,959 (Guire), each patent incorporated herein by reference in its entirety and for all purposes.

Brief Summary Paragraph Right (22):
It is another object of the present invention to make a biochip wherein the biochip has attached upon its surface a patten of nucleic acid polymers such as DNA or RNA immobilized in different locations.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 15. Document ID: US 5736257 A

L1: Entry 15 of 15 File: USPT Apr 7, 1998

DOCUMENT-IDENTIFIER: US 5736257 A
TITLE: Photoactivatable polymers for producing patterned biomolecular assemblies

Brief Summary Paragraph Right (6):
However, currently several broad strategies are being applied to the development of patterned surfaces on which multiple antibodies are immobilized. The first involves keeping the different antibodies physically separate throughout the immobilization procedure. The techniques employed range from simply applying the antibodies in individual stripes using a paintbrush, to microwriting, microstamping or microspotting. These methods are simple and flexible, but do not allow for the production of high resolution (submicron) protein patterns. The second strategy uses microlithography to produce active substrate regions formed by selective removal or photochemical conversion of reactive monolayers to produce discrete regions for antibody immobilization. See Amos, R. A. et al. Surface Modification of Polymers by Photochemical Immobilization-A General Method, The 17th Annual Meeting of the Society for Biomaterials, 1-5 May 1991, Scottsdale, Ariz., incorporated herein by reference in its entirety and for all purposes. See Clapper, D. L. et al., Covalent Immobilization of Cell Adhesion Proteins and Peptides to Promote Cell Attachment and Growth of Biomaterials, The 16th Annual Meeting of the Society for Biomaterials, 20-23 May 1990, Charleston, S.C., incorporated herein by reference in its entirety and for all purposes. See Colby, L. E. et al., Light Activated Polymers for Flexible Surface Modification, Proceedings of the Medical Design & Manufacturing Conference, Jun. 3, 1992, N.Y., N.Y., incorporated herein by reference in its entirety and for all purposes. See Smithson, R. L. W, et al., Ultrathin Film Characterization: Photoreactive Polyacrylamide, 1 Colloids and Surfaces B: Biointerfaces, pp. 349-355 (1993), incorporated herein by reference in its entirety and for all purposes. See Yah, M.; Cai, S. X.; Wybourne, M. N.; Keana, J. F. W. J. Am. Chem. Soc. 115, 814-816, 1993, incorporated herein by reference in its entirety and for all purposes. See also U.S. Pat. Nos. 4,722,906 (Guire); 5,258,041 (Guire); 5,217,492 (Guire); 4,979,959 (Guire), each patent incorporated herein by reference in its entirety and for all purposes. Modification of surfaces for increasd biocompatability as discussed by Amos, Clapper, Guire, Yah, Colby and Smithson, supra, differ from the present invention in that (a) they do not teach photoactivation prior to fabrication of arrays of biomolecules and (b) they do not teach that photoactivatable groups are a part of the structure of the formed photoactivatable polymers. See Bhatia, S. K.; Teixeira, J. L.; Anderson, M.; Shriver-Lake, L. C.; Calvert, J. M.; Georger, J. H.; Hickman, J. J.; Dulcey, C. S.; Schoen, P. E.; Ligler, F. S. Anal. Biochem. 208, 197-205, 1993, incorporated herein by reference in its entirety and for all purposes. See Eggers, M.; Hogan, M.; Reich, R. K.; Lamture, J.; Ehrlich, D.; Hollis, M.; Kosicki, B.; Powdrill, T.; Beattie, K.; Smith, S.; Varma, R.; Gangadharan, R.; Mallik, A.; Burke, B.; Wallace, D. BioTechniques, 17, 516-524, 1994, incorporated herein by reference in its entirety and for all purposes. See also U.S. Pat. Nos. 4,103,073 (McAlear et al.); 4,103,064 (McAlear et al.); 4,562,157 (Lowe et al.), each patent incorporated herein by reference in its entirety and for all purposes. See Ekins, R.; Chu, F.; Biggart, E. Analytica Chemica Acta., 227, 73-96, 1989, incorporated herein by reference in its entirety and for all purposes. Bhatia, Eggers, Lowe, McAlear and Elkins, supra, do not teach deposition and/or patterning of multiple (i.e. different) biomolecules. See also U.S. Pat. Nos. 4,591,570 (Chang), incorporated herein by reference in its entirety and for all purposes. See Kakabakos, S. E.; Christopoulos, T. K.; Diamandis, E. P. Clin. Chem., 38, 338-342, 1992, incorporated herein by reference in its entirety and for all purposes. See Parsons, R. G.; Kowal, R.; LeBlond, D.; Yue, V. T.; Neargarder, L.; Bond, L.; Garcia, D.; Slater, D.; Rogers, P. Clin. Chem. 1993, 39, 1899-1903, incorporated herein by reference in its entirety and for all purposes. Chang, Kakabakos, and Parsons, supra, do not use photoactivation to determine the geometry of biomolecular arrays and do not describe a technique for the fabrication of micron scale biomolecular arrays. See Lopez, G. P.; Biebuyck, H. A.; Whitesides, G. M. Langmuir, 9, 1513-1516, 1993, incorporated herein by reference in its entirety and for all purposes. See Pale-Grosdemange, C.; Simon, E. S.; Prime,

K. L.; Whitesides, G. M. J. Am. Chem. Soc., 113, 12-20, 1991, incorporated herein by reference in its entirety and for all purposes. See Prime, K. L.; Whitesides, G. M. J. Am. Chem. Soc. 115, 10714-10721, 1993, incorporated herein by reference in its entirety and for all purposes. Lopez, Pale-Grosdemange, and Prime, supra, only describe production of biomolecular arrays on gold surfaces via chemisorbed thiols. See Pritchard, D. J. et al., Micron-Scale Patterning of Biological Molecules, 34, No. 1, Angew. Chem. Int. Ed. Engl., pp. 91-93, 1995, incorporated herein by reference in its entirety and for all purposes. Pritchard, supra, describes deposition of two antibodies in distinct locations based on photoactivation of an aryl nitrene linked to biotin wherein the biotin moiety is bound to surface bound avidin. Pritchard has to add the aryl nitrene linked biotin (i.e. photoactivatable cross-linker) after deposition of the avidin on the surface of the substrate. In contrast, according to the presently claimed invention, the photoactivatable compound (e.g. 2,6-DOCA-which can be incorporated in any density or concentration desired) is an integral part of the polymer layer. Furthermore, according to the Pritchard technique, supra, the large size (360 Kd molecular weight) of the avidin limits the density of the aryl nitrene biotin bound to the substrate surface. See Fodor, S. P. A. et al., Light-Directed, Spatially Addressable Parallel Chemical Synthesis, Research Article, pp. 767-773, 15 Feb. 1991, incorporated herein by reference in its entirety and for all purposes. Fodor, supra, describes a method for the deposition of nucleic acid polymers or peptides upon a substrate, respectively. However, the deposition technique of Fodor, supra, requires that the deposition of the nucleic acid polymer or peptide be done one base pair or one amino acid at a time, respectively. See Smithson, R. L. W., et al., Ultrathin Film Characterization: Photoreactive Polyacrylamide, 1 Colloids and Surfaces B: Biointerfaces, pp. 349-355 (1993), incorporated herein by reference in its entirety and for all purposes. See also Wrotnowski, C., Biochip Technology Offers Powerful Tools for Reasearch and Diagnostics, Genetics and Engineering News, 15 November 1994 at page 8, incorporated herein by reference in its entirety and for all purposes. See also U.S. Pat. Nos. 4,591,570 (Chang); 4,751,171 (Ogawa); 4,103,073 (MeAlear et al.); 4,103,064 (MeAlear et al.); 4,562,157 (Lowe et al.); 4,722,906 (Guire); 5,258,041 (Guire); 5,217,492 (Guire); 4,979,959 (Guire), each patent incorporated herein by reference in its entirety and for all purposes.

Brief Summary Paragraph Right (22):
It is another object of the present invention to make a biochip wherein the biochip has attached upon its surface a patten of nucleic acid polymers such as DNA or RNA immobilized in different locations.

Term	Documents
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☐ 1. Document ID: US 6242246 B1

L3: Entry 1 of 1 File: USPT Jun 5, 2001

DOCUMENT-IDENTIFIER: US 6242246 B1
TITLE: Nucleic acid ligand diagnostic Biochip

Detailed Description Paragraph Right (34):
In another embodiment, SELEX will be performed using a pool of Nucleic acids containing a binding site for a particular small molecule. An example of such a small molecule is the caffeine analogue theophylline. Single stranded Nucleic acid ligands against this molecule form a double-stranded stem with a hairpin loop in which the 5' and 3' ends of the molecule are close to one another. This structure only forms in the presence of theophylline. In this embodiment, a candidate mixture of theophylline ligands will be synthesized with random sequence in the hairpin loop. region, and the candidates will then be passed over a solid support, preferably a column, to which theophylline has been attached. The candidate ligands will bind tightly to theophylline, and will become immobilized on the column. The mixture containing Target molecules will be added to the column, and ligands that are eluted will be collected. This will select for ligands that bind their Target molecules in such a way that the ligand will no longer bind to theophylline. Such ligands will be displaced because the adoption of the structure that binds the Target molecule will disrupt the structure that binds the theophylline. The ligands will be refined in the standard ways described in the SELEX patent applications. A Biochip (FIG. 4) will then be fabricated (41) on which theophylline (42) is attached by any of the methods known in the art One or more individual species of the Nucleic acid ligands (43) will then be attached at defined locations on the Biochip, where they bind tightly to the theophylline. Contacting of the Test mixture with the Biochip leads to the displacement (44) from the Biochip of Nucleic acid ligands that bind to their cognate Target molecule (45). The displacement will be detected by any of the means detailed above (46). This technique will be used with any Nucleic acid ligand that forms a hairpin-type structure similar to theophylline, or any other Nucleic acid ligand that can be synthesized with additional random sequence, and will then bind to two different compounds in a mutually exclusive manner, such that the binding of one compound will displace the other.

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